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(54) Vasculoprotecting compositions

(57) The compositions contain an ubiquinone compound and one or more compounds of known vasculoprotecting activity, e.g. of flavanoid, heparinoid, terpenic or glycosidic structure, such as escin, troxerutin, asiaticoside, heparin, delphinidin and tribenoside. The ubiquinone is preferably Coenzyme Q10.

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SPECIFICATION

Vasculoprotecting pharmaceutical compositions

- 5 This invention relates to pharmaceutical compositions for vascular therapy. 5
 Among the vasculoprotecting agents, particularly known are flavonoids, whose effectiveness as capillary-protecting agents, antiedemics and cicatrizants in vasal diseases has been widely described in literature (Bohr D.F. - J. Pharmacol. Exp. Ther., 97-243-1949; Gugler R. - Ges. Arch. Exp. Pathol. Pharm. - 274-R45-1972; Haeger K. - Zbl. Phlebol., 6-526-1967; Rozkoeh K. - Europ. J. Clin. Pharmacol., 3-243-1971; Allen S. - Practitioner, 205-221-1970). 10
 Similar activities were disclosed for heparin and heparinoids (Witte S., Thromb. Diath. Hemorrhag., 2-146-1958; Jacques L. B. - Ann. N. Y. Acad. Sci., 115-781-1969; Nicolaides A.N. - Lancet, 2-890-1972).
 All the flavonoids, at the vasal level, act to regulate the entry of calcium into the cells (Ludwig O. - Med. Welt, 16-1181-1942) and to inhibit any increased effect of lysosomal enzymes, related to pathologic conditions 15
 (Niches P. - Angiologica, 8-297-1971).
 Moreover, it should be pointed out that the synthesis of glycosaminoglycans, which are among the main components of vasal wall and control its hydropexic action as well as ion passage, takes place mainly by activation of Golgi apparatus, whose function is conditioned by the availability of respiratory chain, related to Coenzyme Q₁₀ (Balasz E. - Arthritis-Arthrose Verlag Haan Huber, Bern Wien, 46-1971; Crane F. L. - "Biomedical and Clinical Aspects of Coenzyme Q", Folkers K. Ed., Vol. 1, Elsevier Amsterdam, 1977, p. 3; Lenaz G. - Drugs Exptl. Clin. Res., 10-481-1984). 20
 A deficiency in oxygen diffusion and utilization, as well as tissular hypoxic conditions, have been also indicated as causes of vascular diseases and atherosclerosis (Robertson A.L. - Progr. Biochem. Pharmacol., Vol. 4, p. 305, Karger, Basel, 1968; Zemplyny T. - Symposia Angiologica Santoriana - 4 Int. Symp., 25
 Fribourg-Nylon 1972 - Angiologica, 9-429-1972).
 Coenzyme Q₁₀ is known to control the transport of mitochondrial electrons, and consequently to play a role in oxygen utilization and tissue metabolism, being tissular and cellular energetic processes related to hydrogenion transport (Morton R.A. - Nature, 182-1764-1958; Gale P.H. - Arch. Biochem. Biophys., 93-211-1961). 30
 In fact, Coenzyme Q₁₀ avoids the damages caused by cellular lypoperoxydation, intracellular calcium increase and lysosomal enzyme release, which markedly affect normal cellular and tissular vasal functioning (Lehede A.V. - J. Mol. Cell. Cardiol., 14 (Suppl. 3) 99-1982; Littarru G.P. - Drugs Exptl. Clin. Res., 10-491-1984).
 Now it has surprisingly been found that ubiquinone compounds, particularly Coenzyme Q₁₀, synergetically enhance the activity of known vasculoprotecting agents, particularly chalones, auronos, flavones, 35
 flavanones, flavanols, flavanohols, flavanediols, leukoanthocyanidines, cumarins, hesperidins, catechins, anthocyanidines, natural or semisynthetic derivatives thereof, or vegetal extracts containing them.
 According to the present invention we provide pharmaceutical compositions containing as the active ingredient an ubiquinone compound together with known compounds suitable for vascular therapy.
 Examples of said vasculoprotecting compounds are those having flavonoid, terpanic, glycosidic and 40
 heparinoid structures, such as escin, rutin, troxerutin, diosmin, asiaticoside, hesperidin, tribenoside, etc.
 We have found that the components of the compositions according to the invention display a synergetic action on the regulation of vascular activity and permeability.
 Moreover, said compositions prevent trophic and metabolic tissular changes as well as those from anoxic conditions, due to impaired vascularization. 45
 By means of the combination of the present invention, a marked increased in therapeutic action is obtained, in comparison with the one of the single components, without toxic or side-effects.
 The pharmaco-toxicologic tests carried out will be hereinafter described, in order to illustrate the advantages of the compositions of the present invention.
 Coenzyme Q₁₀ is known to have a poor toxicity, its DL₅₀ in rats and mice being respectively higher than 500 50
 and 250 mg/kg by intraperitoneal administration, and higher than 4 g/kg by subcutaneous administration.
 Flavonoids and heparinoids are also known to be poorly toxic, and the combination thereof with Coenzyme Q₁₀ shows no changes in the toxicity values of the components. 1:1 Combination of Coenzyme Q₁₀ and anthocyanine, hydroxyethylrutoside or catechin, showed DL₅₀ values higher than 1 g/kg in both rats and mice, by oral administration.
 55 Also the chronic toxicity tests carried out in the rat by oral daily administration of the above combinations in 1:1 ratio for 30 consecutive days showed no pathologic changes in the body weight and in hemathological and biochemical parameters.
 On the contrary, the above combinations proved to be surprisingly effective in different pharmacological tests, such as wound-healing time in experimental wounds in the rabbit, rupture resistance of cicatrices in the 60
 mouse, antiedemic activity in the rat, activity on capillary permeability and ergotamine arteritis in the rat.
 In all the above tests a marked synergism between Coenzyme Q₁₀ and the other vasoprotecting compounds was evidenced, the obtained results being surprisingly more favourable than the ones obtained using the single components.
 The tests were carried out combining Coenzyme Q₁₀ with O-(β -hydroxyethylrutoside), escin (a saponin 65
 from Esculus hippocastanum), tribenoside (ethyl 3,5,8-tri-O-benzyl- β -glycofuronoside), delphinidin

(anthocyanidin), and total extract of *Centella asiatica* (asiaticoside).

The tests on wound healing activity of the compositions of the invention were carried out on cutaneous wounds in the rat orally treated with prednisolone, according to the procedure of J.J. Morton (Morton J.J.P., Malone M.H. - Arch. Int. Pharmacodyn., 196-117-1972).

- 5 The cicatrization of the cutis of the back of the rat previously scarified was delayed by oral treatment with 0.25 mg/kg of prednisolone. 5

The test composition was applied on the wound, after appropriate suspension at different concentrations.

The area of the wound on the third day of treatment was measured: the results reported in the following Table 1 evidence a marked synergetic action of the compositions of the invention.

10

TABLE 1

10

	<i>Compound</i>	<i>Dose mg/cm² cutis</i>	<i>% Reduction</i>	
15	A	100	22	15
	B	10	15	
20	C	50	11	20
	D	25	18	
	E	25	12	
25	A + B	100 + 10	65	25
	A + C	100 + 50	40	
30	A + D	100 + 25	56	30
	A + E	100 + 25	63	

A = Coenzyme Q₁₀

B = Delphinidin

35 C = Escin

35

D = Tribenoside

E = Asiaticoside.

Oral administration of the compositions of the invention also surprisingly increased the rupture resistance of scars induced in the mouse by incision of cutis of the back. The treatment was continued during 3 consecutive days after surgical suturation of the wound, after this period the cutis portion containing the scar was removed, one end thereof was fixed to a support and the other one was subjected to continuous traction (110 g/minute). The rupture strength results are reported in Table 2 hereinbelow.

TABLE 2

Compound	Dose mg/kg (per os)	% Rupture resistance (in grams)
10 A	25	19
15 B	100	21
C	25	16
D	50	15
20 E	25	13
A + B	25 + 100	75
25 A + C	25 + 25	82
A + D	25 + 50	80
A + E	25 + 25	95

30 A, B, C, D, E = *vide* Table 1.

The capillary resistance tests were carried out according to the procedure of Charlier R. (Charlier R., Hosslet A., Colot M., - Arch. Int. Physiol. Biochem., 71-1-1963), by oral treatment for 3 consecutive days of rats, previously fed for 2 weeks with a diet lacking in vitamin P.

35 The increase of capillary resistance was measured by means of a mercury vacuumeter.
The results are reported in following Table 3.

TABLE 3

Compound	Dose mg/kg (per os)	Capillary resistance % increase
40 A	25	2.5
45 B	100	12.2
C	25	9.5
50 D	50	12.9
F	50	11.5
A + B	25 + 100	35.5
55 A + C	25 + 25	24.3
A + D	25 + 50	32.4
60 A + F	25 + 50	25.5

A to D = *vide* Table 1.

F = Hydroxyethylrutoside.

Also in this test a marked synergetic action was evidenced.

65 The pharmaceutical compositions of the invention may be prepared according to conventional procedures

of pharmaceutical technique, using pharmaceutically acceptable carriers or diluents.
Non-limiting examples of suitable compositions of the invention are reported hereinbelow.

Tablets

- | | | |
|----|--|----|
| 5 | - Coenzyme Q ₁₀ 10 mg + escin 20 mg | 5 |
| | - Coenzyme Q ₁₀ 50 mg + escin 20 mg | |
| | - Coenzyme Q ₁₀ 10 mg + hydroxyethylrutoside 300 mg | |
| | - Coenzyme Q ₁₀ 50 mg + hydroxyethylrutoside 500 mg | |
| | - Coenzyme Q ₁₀ 10 mg + asiaticoside 10 mg | 10 |
| 10 | - Coenzyme Q ₁₀ 50 mg + asiaticoside 10 mg | |
| | - Coenzyme Q ₁₀ 10 mg + tribenoside 400 mg | |
| | - Coenzyme Q ₁₀ 50 mg + tribenoside 500 mg | |
| | - Coenzyme Q ₁₀ 10 mg + delphinidin 100 mg | |
| | - Coenzyme Q ₁₀ 50 mg + delphinidin 200 mg. | 15 |

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Sugar-coated pills

- | | | |
|----|--|----|
| | - Coenzyme Q ₁₀ 10 mg + escin 20 mg | |
| | - Coenzyme Q ₁₀ 50 mg + hydroxyethylrutoside 500 mg | |
| | - Coenzyme Q ₁₀ 10 mg + tribenoside 500 mg | 20 |
| 20 | - Coenzyme Q ₁₀ 50 mg + tribenoside 500 mg | |

Capsules

- | | | |
|----|---|----|
| | - Coenzyme Q ₁₀ 10 mg + escin 20 mg | |
| | - Coenzyme Q ₁₀ 10 mg + tribenoside 400 mg | 25 |
| 25 | - Coenzyme Q ₁₀ 50 mg + tribenoside 500 mg | |

Creams

- | | | |
|----|---|----|
| | - Coenzyme Q ₁₀ 1% + escin 1% | |
| | - Coenzyme Q ₁₀ 1% + hydroxyethylrutoside 2% | 30 |
| 30 | - Coenzyme Q ₁₀ 1% + asiaticoside 1% | |
| | - Coenzyme Q ₁₀ 1% + tribenoside 1% | |
| | - Coenzyme Q ₁₀ 1% + delphinidin 1%. | |

Ointments

- | | | |
|----|---|----|
| 35 | - Coenzyme Q ₁₀ 1% + escin 1% | 35 |
| | - Coenzyme Q ₁₀ 1% + sodium heparin 10,000 IU/100 g of ointment | |
| | - Coenzyme Q ₁₀ 1% + natural heparinoid 70,000 IU/g | |
| | - Coenzyme Q ₁₀ 1% + sulfate glucuronylglycosaminoglycane (heparinoid) 200 mg, equal to 400 UHC. | 40 |

Suppositories

- | | | |
|----|--|----|
| 40 | - Coenzyme Q ₁₀ 50 mg + escin 50 mg | |
| | - Coenzyme Q ₁₀ 100 mg + hydroxyethylrutoside 500 mg | |
| | - Coenzyme Q ₁₀ 50 mg + total extract of Centella asiatica (equal to 10 mg of asiaticoside) 50 mg | |
| | - Coenzyme Q ₁₀ 100 mg + tribenoside 1,000 mg | 45 |
| 45 | - Coenzyme Q ₁₀ 100 mg + delphinidin 400 mg. | |

The compositions of the invention may suitably be administered 2 to 4 times daily, even for prolonged treatment, at dosages depending on age, weight and general conditions of the patient.

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50 CLAIMS

1. A pharmaceutical composition having vasculoprotecting activity, containing a ubiquinone compound and at least one other compound having known vasculoprotecting activity.
2. A pharmaceutical composition as claimed in claim 1, wherein the ubiquinone compound is Coenzyme Q₁₀.
3. A pharmaceutical composition as claimed in claim 1 or 2, wherein the known compound having vasculoprotecting activity is selected from compounds having flavanoid, heparinoid, terpenic or glycosidic structure.
4. A pharmaceutical composition as claimed in claim 3, wherein the compound having known vasal protecting activity is selected from the groups comprising: rutin, O-(β -hydroxy-ethylrutoside), delphinidin, hesperidin, diosmin, asiaticoside, catechin, heparin, heparinoids, escin, ruscogenin, tribenoside, sodium 2-phenyl-5,7-dioxyacetate and benzo- γ -pyrone.
5. A pharmaceutical composition as claimed in any one of claims 1 to 4, wherein Coenzyme Q₁₀ and vasculoprotecting compound are present in a ratio ranging from 1:1 to 1:1000.
6. A pharmaceutical composition as claimed in any one of claims 1 to 5, for oral, parenteral, rectal or

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topical administration.

7. A pharmaceutical composition as claimed in claim 6, in the form of capsules, tablets, syrup, granulate, sterile solution, ointment, cream, lotion, gel or suppositories.

8. A pharmaceutical composition substantially as described herein and exemplified.

5 9. A pharmaceutical composition according to any one of the preceding claims for use in vascular therapy.

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